STATISTICAL ANALYSIS PLAN

APD334-308

A PHASE 3, DOUBLE-BLIND, PLACEBO-CONTROLLED, 40-WEEK EXTENSION STUDY TO ASSESS THE EFFICACY AND SAFETY OF ETRASIMOD IN JAPANESE SUBJECTS WITH MODERATELY TO SEVERELY ACTIVE ULCERATIVE COLITIS

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

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Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

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MODIFICATION HISTORY

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Draft 0.1	16Aug2021	PPD	Not Applicable – First Version
	14Apr2022	PPD	Adding Efficacy Section
	20Jun2022	PPD	Removing hypothesis testing/multiple imputations/sensitivity analyses
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	03Aug2022	PPD	Modified Key Secondary Efficacy outcomes to be a bullet form presentation./ Simplified Exploratory Efficacy outcomes./ Concomitant medication./ Added some terms to List of Abbreviation.
	26Sep2022	PPD	Finalized.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Explanation
5-ASA	5-aminosalicylic acid
AE	adverse event
AESI	adverse events of special interest
ALC	absolute lymphocyte count
ALP	Alkaline phosphatase
ALT	alanine aminotransferase
APD334	etrasimod
Arena	Arena Pharmaceuticals, Inc.
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AV	atrioventricular
β-hCG	beta-human chorionic gonadotropin
BLQ	below the limit of quantification
BMI	Body Mass Index
bpm	beats per minute
CI	confidence interval
CM	concomitant medication
CMH	Cochran-Mantel-Haenszel
Covid-19	coronavirus disease 2019
CR	Copy Reference
CRP	C-reactive protein
CS	Clinically Significant
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
$C_{trough,ss}$	Average steady-state tough plasma concentration
CV	coefficient of variation
DBP	Diastolic blood pressure
DLCO	diffusing capacity of the lungs for carbon monoxide
EAIR	exposure-adjusted incidence rate

Abbreviation	Explanation
ECG	electrocardiogram
eCRF	electronic caser report form
eDISH	evaluation of Drug-Induced Serious Hepatotoxicity
CCI	[redacted]
ES	endoscopic score
FAS	Full Analysis Set
FCP	fecal calprotectin
FCS	fully conditional specification
FDA	Food and Drug Administration
FEF	Forced Expiratory Flow
FEV1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
GGT	gamma-glutamyl transferase
HR	heart rate
HRQoL	Health-Related Quality of Life
hs-CRP	high-sensitivity C-reactive protein
IBDQ	Inflammatory Bowel Disease Questionnaire
ICF	informed consent form
JAK	Janus kinase
LLQ	limit of quantification
LOESS	locally estimated scatterplot smoothing
LS	Least squares
MAR	missing at random
MCMC	Markov Chain Monte Carlo
MCS	mental component summary
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	modified Full Analysis Set
MMRM	mixed-effect model with repeated measures
MMS	modified Mayo score
MNAR	missing not at random
NCS	Not Clinically Significant

Abbreviation	Explanation
NHI	Nancy Histologic Index
NRI	Nonresponder imputation
NRS	Numeric Rating Scale
OCT	optical coherence tomography
OLE	open-label extension
PCS	physical component summary
PFT	pulmonary function test
PGA	Physicians Global Assessment
PK	pharmacokinetics
PRES	posterior reversible encephalopathy syndrome
PT	preferred term
RB	rectal bleeding
CCI	[redacted]
RNA	ribonucleic acid
SAE	serious adverse events
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SD	standard deviation
SDTM	Study Data Tabulation Model
SF	stool frequency
SF-36	36-Item Short Form Health Survey
SI	International System of Units
SOC	system organ class
SS	Steady state
TB	Tuberculosis
TEAE	treatment-emergent adverse event
TLC	Total Lung Capacity
TME	targeted medical event
TMS	total Mayo score
TNFα	tumor necrosis factor alpha
UC	ulcerative colitis

Abbreviation	Explanation
UC-PRO/SS	ulcerative colitis patient-reported outcomes signs and symptoms
ULN	Upper limit of normal
ULQ	upper limit of quantification
WHO	World Health Organization
WPAI-UC	Work Productivity and Activity Impairment Questionnaire – Ulcerative Colitis

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical rationale, methods, rules and conventions to be used in the presentation and analysis of efficacy, safety, pharmacokinetic, health-related subject-reported outcome and biomarker data for Protocol APD334-308. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed (ICH 1998). This SAP is based on protocol version Original 0.0, dated 15 April 2020.

2. STUDY Objectives

2.1. Primary Objective

The primary objective is to assess the efficacy of etrasimod on clinical remission in Japanese subjects with moderately to severely active ulcerative colitis (UC) at timepoints up to 52 weeks of treatment (12 weeks in Study APD334-302 plus 40 weeks in Study APD334-308).

2.2. Secondary Objectives

The secondary objective is to assess the efficacy of etrasimod on clinical response, symptomatic response and remission, endoscopic changes, corticosteroid-free remission, and mucosal healing in Japanese subjects with moderately to severely active UC at timepoints up to 52 weeks of treatment (12 weeks in Study APD334-302 plus 40 weeks in Study APD334-308).

2.3. Safety Objective

The safety objective is to assess the long-term safety of etrasimod in Japanese subjects with moderately to severely active UC after daily doses of 2 mg for up to 52 weeks (12 weeks in Study APD334-302 plus 40 weeks in Study APD334-308).

2.4. Other Objectives

Other objectives include evaluation of etrasimod pharmacokinetics (PK) and the effect of etrasimod on health-related subject-reported outcomes and biomarkers.

2.5. Estimands

The primary and key secondary efficacy estimands to support regulatory decisions are described in Table 1. The analyses will be performed on the Full Analysis Set (FAS) as defined in Section 5.3. Other secondary efficacy variables (specified in Section 16.3.1) will have the population, intercurrent event handling strategy and population-level summary measure similar to the primary estimand. Supplementary analyses for the primary and the key secondary estimands will be performed on the modified Full Analysis Set (mFAS) and the Per Protocol populations, respectively .

Table 1 List of Primary and Key Secondary Estimands

Estimand	Definition	Attribute			
		Population	**Variable/Endpoint**	**Intercurrent Event Handling Strategy**	**Population-Level Summary Measure**
Primary Estimand 1	Efficacy of etrasimod on clinical remission at Week 52	Enrolled subjects who receive at least 1 dose of etrasimod	The proportion of subjects with SF = 0 (or = 1 with a ≥ 1-point decrease from Baseline in APD334-302), RB = 0, and ES ≤ 1 (excluding friability) at Week 52	Subjects with missing data for any reason (including discontinuation due to lack of efficacy or adverse event related to UC) or any of the 3 intercurrent events[a] before the efficacy assessment will be treated as nonresponders.	Difference between etrasimod and placebo in proportion of responders at Week 52
Key Secondary Estimand 1	Efficacy of etrasimod on endoscopic improvement at Week 52	Enrolled subjects who receive at least 1 dose of etrasimod	The proportion of subjects with ES of ≤ 1 (excluding friability) at Week 52	Same as the intercurrent event handling strategy for the primary estimand	Difference between etrasimod and placebo in proportion of responders at Week 52
Key Secondary Estimand 2	Efficacy of etrasimod on symptomatic remission at Week 52	Enrolled subjects who receive at least 1 dose of etrasimod	The proportion of subjects with SF = 0 (or = 1 with a ≥ 1-point decrease from Baseline in APD334-302) and RB = 0 at Week 52.	Same as the intercurrent event handling strategy for the primary estimand	Difference between etrasimod and placebo in proportion of responders at Week 52
Key Secondary Estimand 3	Efficacy of etrasimod on corticosteroid-free clinical remission at Week 52	Enrolled subjects who receive at least 1 dose of etrasimod	The proportion of subjects with clinical remission at Week 52, while not receiving corticosteroids for 12 or more weeks in the 40-Week Treatment Period	Same as the intercurrent event handling strategy for the primary estimand	Difference between etrasimod and placebo in proportion of responders at Week 52
Key Secondary Estimand 4	Efficacy of etrasimod on mucosal healing at Week 52	Enrolled subjects who receive at least 1 dose of etrasimod	The proportion of subjects with ES of ≤ 1 (excluding friability) with histologic remission measured by a Geboes Index score < 2.0 at Week 52	Same as the intercurrent event handling strategy for the primary estimand	Difference between etrasimod and placebo in proportion of responders at Week 52

Estimand	Definition	Attribute			
		Population	**Variable/Endpoint**	**Intercurrent Event Handling Strategy**	**Population-Level Summary Measure**
Key Secondary Estimand 5	Efficacy of etrasimod on sustained clinical remission	Enrolled subjects who receive at least 1 dose of etrasimod	The proportion of subjects with sustained clinical remission (clinical remission at both Weeks 12 and 52)	Same as the intercurrent event handling strategy for the primary estimand	Difference between etrasimod and placebo in proportion of responders

[a] Intercurrent events include: 1) initiate a rescue medication for UC, 2) have an increase in dose over Baseline levels in their existing UC medication, or 3) have colectomy or ileostomy before the efficacy assessment.

This SAP will analyze on the data collected in APD334-308 (from Week 16 to Week 52). The scope of analysis will be specified in Table/Listing/Figure shells. To fully address study primary objective "to assess the efficacy of etrasimod on clinical remission in Japanese subjects with moderately to severely active ulcerative colitis (UC) at timepoints up to 52 weeks of treatment (12 weeks in Study APD334-302 plus 40 weeks in Study APD334-308)", after database lock and treatment unblinding, an integrated analysis of Study APD334-302 and Study APD334-308 will be performed for all Japanese subjects who had enrolled in ADP334-302 and covers the complete data from APD334-302 and to APD334-308.

3. STUDY Design

3.1. General Description

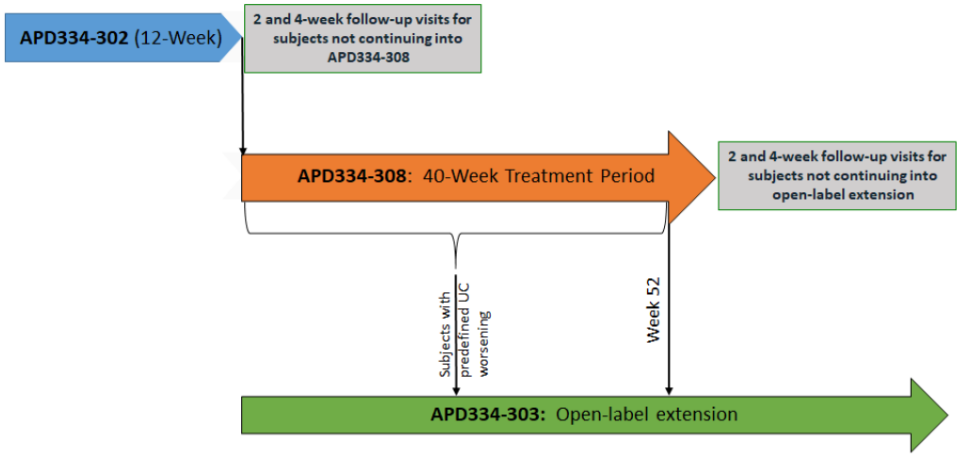
This is a multicenter, double-blind, placebo-controlled extension study of APD334-302 (12-week, randomized, double-blind, placebo-controlled induction study) to evaluate the efficacy and safety of etrasimod 2 mg in Japanese subjects with moderately to severely active UC. The study consists of a 40-Week Treatment Period and a 4-Week Follow-Up Period (Figure 1).

Japanese subjects who completed the Week 12 visit of Study APD334-302 are eligible for Study APD334-308. The Week 12 visit of Study APD334-302 serves as the Day 1 visit of this study. Subjects will continue with the same blinded treatment assigned in Study APD334-302 for a total treatment duration of 52 weeks (12 weeks in Study APD334-302 plus 40 weeks in Study APD334-308).

Disease worsening will be monitored by Investigators through the treatment period of Study APD334-308. Subjects who either experience disease worsening or complete all study procedures at Week 52 will have the option to enroll into the APD334-303 OLE study if they meet all eligibility criteria.

Subjects who discontinue from the study and do not participate in the OLE study will have 2-Week and 4-Week Follow-Up visits after the last on-treatment visit/Early Termination visit.

Figure 1 Study Design



3.2. Schedule of Events

Schedule of events can be found in Appendix Table 7 of the protocol.

3.3. Changes to Analysis from Protocol

Note that Ulcerative Colitis Patient-Reported Outcomes Signs and Symptoms (UC-PRO/SS) was never implemented in Study APD334-308. Therefore, no summary is planned.

Protocol Section 10.12.1 Efficacy Analysis specified "The primary analysis of the proportion-based efficacy endpoints will be carried out using the Cochran-Mantel-Haenszel (CMH) method, stratified by (a) naive to biologic or JAK inhibitor therapy at APD334-302 study entry (yes or no), (b) baseline corticosteroid use (yes or no), and (c) baseline disease activity (MMS: 4 to 6 or 7 to 9)." Due to the limited number of subjects enrolled in APD334-308 and globally stratified randomization do not control for treatment balance in Japanese subjects, above mentioned CMH method was remove from for APD334-308 efficacy analyses.

4. PLANNED ANALYSES

The following analyses will be performed for this study:

- Final Analysis for APD334-308 data only
- An integrated analysis that covers the complete data from APD334-302 and to APD334-308. This analysis will be specified in a separate analysis plan

4.1. Interim Analysis

There is no planned interim analysis for this study.

4.2. Final Analysis

All final, planned analyses identified in this SAP will be performed by IQVIA Biostatistics following Sponsor (Arena Pharmaceuticals, Inc., hereafter referred to as Arena) authorization of the SAP, database lock, analysis sets, and unblinding of treatment. After Arena has authorized breaking of the study blind, the final analysis will be performed.

Any, post-hoc, CCI analyses completed to support planned study analyses, which were not identified in this SAP, will be documented and reported in the clinical study report (CSR). Any results from these unplanned analyses will also be clearly identified in the text of the CSR (ICH, 1995).

5. ANALYSIS SETS

Agreement and authorization of subjects included/excluded from each analysis set will be conducted prior to the unblinding of the study.

5.1. SCREENED SET

The Screened Set will consist of all subjects who sign informed consent to participate in the study. No analysis is planned in this set.

5.2. RANDOMIZED SET

The Randomized Set will consist of all Japanese subjects who are randomized to study treatment at the start of Study APD334-302. No analysis is planned in this set.

5.3. FULL ANALYSIS SET [FAS]

The FAS will consist of all enrolled subjects who signed informed consent form and receive at least 1 dose of study treatment during Study APD334-308. Subjects will be summarized by the treatment group to which they were randomized in Study APD334-302, regardless of the treatment actually received during Study APD334-308.

5.4. PER PROTOCOL SET

Due to a small number of subjects in APD334-308 who meet the Per Protocol criteria, efficacy analyses in Per Protocol Set will not be performed.

5.5. MODIFIED FULL ANALYSIS SET

The mFAS will consist of all enrolled subjects who receive at least 1 dose of study treatment and have a Baseline and at least 1 post enrollment measurement in APD334-308. Subjects will be summarized by treatment to which they were randomized, regardless of treatment actually received. Note that the mFAS can vary between endpoints since some subjects may have the data needed for inclusion in the mFAS for some endpoints, but not other endpoints. Also note, since the Mayo component scores on the disease worsening CRF are manually entered by sites from another CRF, these scores will not be used in the derivation of mFAS for measurement of either MMS or any of its component scores.

5.6. SAFETY SET

The Safety Set will include all subjects who receive at least 1 dose of study treatment in Study APD334-308. For this set, subjects will be analyzed according to the treatment received, regardless of randomization. The Safety Set will be used for all safety analyses.

5.7. PHARMACOKINETIC SET

The Pharmacokinetic Set will include all subjects in the Safety Set with at least 1 quantifiable post-dose etrasimod concentration which is not impacted by protocol violations or events with potential to affect the etrasimod concentration.

6. GENERAL CONSIDERATIONS

6.1. Reference Start Date and Study Day

Study Day will be calculated from the reference start date and will be used to show start/stop day of assessments and events. Reference start date is defined as the date of first dose (Day 1 in study APD334-302) will appear in every listing where an assessment date or event date appears.

- If the date of the event is on or after the reference date, then:

  Study Day = (date of event – reference date) + 1

- If the date of the event is prior to the reference date, then:

  Study Day = (date of event – reference date)

In the situation where the event date is partial or missing, event dates will be displayed as partial or missing, Study Day and any corresponding durations will appear missing in the listings.

6.2. Baseline

Subjects in Study APD334-308 will continue receiving the same study treatment of Study APD334-302. Unless otherwise specified, analysis baseline for efficacy and safety (for example in change from baseline analysis) is defined as the last non-missing measurement taken prior to the date of first dose in Study APD334-302 (including unscheduled assessments). If measurements include time (except for health-related quality of life [HRQoL] instruments), the date/time will be used to define Baseline. Otherwise, only dates will be compared. For HRQoL instruments, only the date will be used to derive Baseline. In the case where the last non-missing measurement and the date of first dose coincide and time is not collected, if the measurement was planned in the protocol to be done prior to the date of first dose, that measurement will be considered in defining Baseline.

6.3. Retests, Unscheduled Visits and Early Termination Data

For by-visit analyses and summaries, efficacy, safety, HRQoL, and biomarkers data (including scheduled, retests, unscheduled, and early termination) will be assigned to visits after the application of the windowing conventions described in Section 6.4. All measurements will be considered in summaries of abnormalities or worst-case values post Baseline.
Listings will include scheduled, unscheduled, retest, and early termination data.

6.4. Windowing Conventions

All scheduled study visits are defined relative to Study Day 1 in ADP334-302, the date of first dose in Study APD334-302. Scheduled visit windows are defined in Study APD334-308 Protocol Appendix 1. A windowing convention will be used to determine the analysis visit value for a given measurement and will be applicable for all by-visit summaries and analyses for efficacy and safety data. Refer to Table 2 for specific visit windows.

Table 2 Visit Windows for Efficacy and Safety Analyses

For all efficacy (except endoscopy/MMS/histology), efficacy-related biomarkers, safety labs and vital signs.	
Scheduled Study Visit (Protocol Scheduled Day)	**Analysis Visit Window (Study Day)**
Baseline in Study APD334-302	≤ 1
Week 12 (Day 85 ± 3) in Study APD334-302	72 to 99
Week 16 (Day 113 ± 7)	100 to 127
Week 20 (Day 141 ± 7)	128 to 155
Week 24 (Day 169 ± 7)	156 to 197
Week 32 (Day 225 ± 7)	198 to 253
Week 40 (Day 281 ± 7)	254 to 309

Week 48 (Day 337 ± 7)	310 to 351
Week 52 (Day 365 ± 7)	> 351
For endoscopy/MMS/histology/all composite endpoints that include an endoscopy component and/or RB/SF component, physician's global assessment, health-related quality of life, ECGs, OCT, and PFT.	
Scheduled Study Visit (Protocol Scheduled Day)	**Analysis Visit Window (Study Day)**
Baseline in Study APD334-302	≤ 1
Week 12 (Day 85 ± 3)[b] in Study APD334-302	66 to 113 (66 to 141 for assessments impacted by COVID-19 pandemic)[c]
Week 32 (Day 225 ± 7) [PFT only]	198 to 253 (198 to 281 for assessments impacted by COVID-19 pandemic)[c]
Week 52 (Day 365 ± 7)[b]	337 to 393 (337 to 421 for assessments impacted by COVID-19 pandemic)[c]

[a] Applicable only for subjects who required extended monitoring on Day 2 for vital signs and ECGs.
[b] Applicable to all Week 12 and Week 52 efficacy endpoints based on any component of Mayo clinic score, such as clinical remission and symptomatic remission. Protocol visit window for PFT and OCT at Week 12 is Day 85 ± 7 .
[c] Assessments impacted by COVID-19 pandemic are reported in the Date of Visit eCRF.
ECG, electrocardiogram; eCRF, electronic case report form; MMS, modified Mayo score; OCT, optical coherence tomography; PFT, pulmonary function test; RB, rectal bleeding; SF, stool frequency

For cardiac remonitoring upon treatment reinitiation after Day 2, as manifested by more than 1 timed measurement in vital signs or electrocardiogram (ECG) parameters on the same collection date of an unscheduled visit, measurement will be mapped to analysis visit of Cardiac Remonitoring 1, Cardiac Remonitoring 2, etc. in the respective analysis dataset. For analysis, each timed measurement will be programmatically assigned to the nearest hourly timepoint (e.g., Predose, 1-hour Postdose) based on their relationship to the dosing time on the same day. If the dosing date/time on the same day is missing, the timepoint will remain missing. Once mapped, these timed measurements from cardiac remonitoring visits will not be considered for any other analysis visit.

Windowing will be applied prior to any missing data calculations. The last non-missing measurement taken prior to Day 1 (including unscheduled assessments) will be labeled as "Baseline". Unless stated otherwise, data from all visits including scheduled, unscheduled, and ET visits will be eligible for allocation to an analysis visit. The 2-Week and 4-Week Follow-Up visits will not be included in the visit windows and will be summarized separately without any window applied.

If one or more results for a variable are assigned to the same analysis visit, the result with the date closest to the protocol scheduled day will be used in the analysis, except for component subscores of MMS or TMS, in which case, the composite score and component subscores from the same date will be used in the analysis. If 2 measurements in the same analysis visit window are equidistant from the protocol scheduled study day, the earliest measurement will be used in the analysis. If multiple assessments are available on the same day, then the average of the assessment will be used in the analysis, except for laboratory and ECG data where the

assessment at the earliest time of the same day will be used. If both central and local assessments of the same ECG or lab test are available on the same day, the central result will take precedence over the local result.

For the overlapping visit windows at Week 48 and Week 52, Week 52 will take priority.

6.5. Statistical Tests

Due to the limited number of subjects anticipated to enroll in this study and central randomization not designed to control for allocation ratio in Japan. Point estimate with 95% confidence intervals (CIs) and nominal p-values (2-sided) will be reported.

6.6. Common Calculations

For quantitative measurements:

- Change from Baseline = Test Value at Visit X – Baseline Value
- Percent change from Baseline = ((Test Value at Visit X – Baseline Value) / Baseline Value) × 100
- Proportion at Visit X = Number of subjects satisfying criteria at Visit X / Total number of subjects at Visit X

6.7. General Study Information

A general table with summary of study information will be generated, including the date of first subject signed informed consent form (ICF), the last subject visit date, and the database lock date. All analyses will be conducted using SAS® (v9.4 or later, SAS Institute Inc., Cary, NC).

7. DETERMINATION OF SAMPLE SIZE

There is no formal sample size estimation for Study APD334-308. The number of subjects to be enrolled in this study was determined by number of Japanese subjects enrolled in Study APD334-302, and those subjects were eligible to enroll according to Study APD334-308 protocol.

8. STATISTICAL CONSIDERATIONS

8.1. Multicenter Studies

Study APD334-302, the parent study of ADP334-308, was conducted by multiple investigators at multiple centers internationally. Randomization to treatment groups is stratified by:

- Naïve to biologic/JAK inhibitor therapy at APD334-302 study entry (Yes/No)

- Baseline corticosteroid use (Yes/No)
- Baseline disease activity (MMS: 4 to 6 or 7 to 9)

There will be no adjustment for investigational site for this study.

8.2. Adjustments for Covariates and Factors to be Included in Analyses

Due to the limited number of subjects enrolled in this study and central randomization did not control treatment balance in Japanese subjects, unless otherwise specified, only endpoint Baseline measures are used as covariate in the analyses. For details of their inclusion in the models, refer to the specific analysis section.

8.3. Missing data

Missing adverse event (AE) relationship to study drug and AE seriousness will be imputed as described in Section 18.1.1.2 and Section 18.1.3, respectively. Partial or missing AE start dates and concomitant medication start dates will also be imputed as described in APPENDIX 2. No other missing safety data will be imputed.

Missing efficacy data will be handled as described in Section 16.1.2, Section 16.2.2, and Section 16.3.2. In the primary analysis of the primary endpoint and main analyses of all binary responder-type endpoints, all subjects with missing data, regardless of reason for missingness, will be considered as non-responders. In the main analysis of continuous or score endpoints, such as biomarker measures, urgency Numeric Rating Scale (NRS), abdominal pain NRS, and health related quality of life measures, subjects with missing data will be handled using observed cases only.

8.4. Multiple Comparisons/ Multiplicity

There will be no adjustments for multiplicity. Due to the limited number of subjects anticipated to enroll in this study. Point estimate with 95% confidence intervals (CIs) and nominal p-values (2-sided) will be reported.

8.5. Subgroup Analyses

The following subgroups will be assessed for the primary and key secondary endpoints. Baseline is referring to APD334-302:

- Sex (Female/Male)
- Age ($\leq$ or > Median age, and < or $\geq$ 65). This refers to age collected at Screening in Study APD334-302.
- Baseline oral corticosteroid usage (Yes/No)
- Naïve to biologic/JAK inhibitor therapy at APD334-302 study entry (Yes/No)

- Baseline disease activity (MMS: 4 to 6 or 7 to 9)
- Baseline fecal calprotectin (≤ or > median value)
- Baseline total Mayo score (≤ or > 8)
- Duration of UC (≤ or > Median)
- Extent of disease (Proctosigmoiditis/Left-sided colitis, Pancolitis, Proctitis as reported on the eCRF)
    - Proctitis (Yes or No, based on central read)
    - Prior UC treatment of oral 5-aminosalicylic acid (5-ASA) only (Yes or No)
    - Prior UC treatment failure of oral 5-ASA only (Yes or No)
    - Number of prior biologic or JAK inhibitor therapies (1 or > 1)
    - Prior UC treatment failure of anti-tumor necrosis factor alpha (anti-TNFα) (Yes or No)

Additional subgroups may be assessed, if deemed necessary. The medians will be derived based on the FAS for all subgroups cut at the median.

9. OUTPUT PRESENTATIONS

APPENDIX 1APPENDIX 1 contains conventions for presentation of data in outputs.

10. DISPOSITION AND PROTOCOL DEVIATIONS

All subjects who provide informed consent will be accounted for in this study. Inclusion criteria not met and exclusion criteria met will be listed.

Among the enrolled subjects, the number and percent of subjects who completed/ discontinued treatment, reasons off treatment, the number and percent of subjects who completed/discontinued the study, and reasons off study will be summarized. The number and percent of subjects in each analysis set will be summarized for all enrolled subjects. A listing of subjects whose blind was broken during Study APD334-308 will be provided. The number of subjects whose visit was impacted by the COVID-19 pandemic per eCRF will also be summarized by nominal visit.

During site monitoring, protocol deviations will be graded as Critical, Major or Minor. According to ICH E3 and ICH E3(R1), important protocol deviations are a subset of protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a subject's rights, safety, or well-being (ICH 1995, ICH 2012). For example, important protocol deviations might include enrolling subjects in violation of key eligibility criteria designed to ensure a specific subject population or failing to collect data necessary to interpret primary endpoints, as this may compromise the scientific value of the study.

During the review of all reported deviations, important deviations related to study inclusion or exclusion criteria, conduct of the study, patient management or patient assessment will be identified. Where relevant the importance of a potentially important protocol deviations will be assessed in the context of the study's estimands to evaluate potential impact.
All important protocol deviations will be summarized for the FAS in the following categories in descending frequency in the etrasimod group.
All protocol deviations will be listed, including whether a deviation was impacted by the COVID-19 pandemic (Yes or No). Protocol deviation categories include but are not limited to the following:

- Informed Consent
- Eligibility and Entry Criteria
- Concomitant Medication
- Laboratory Assessment
- Study Procedures
- Serious Adverse Event
- Visit Schedule
- Investigational Product Compliance
- Efficacy
- Administrative
- Source Document
- Regulatory or Ethics Approvals
- Other

Important protocol deviations will also be summarized by whether they were impacted by the COVID-19 pandemic (Yes or No). Additionally, a summary of missing endoscopy regardless of reason and missing endoscopy due to visit impacted by the COVID-19 pandemic will be presented by visit.

11. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

The following demographic data and Baseline characteristics reported in the Study APD334-302 will be summarized by treatment group for the FAS.

- Age on consent (years)
- Sex

- Woman of childbearing potential (Yes/No)
- Height (cm)
- Weight (kg)
- Body Mass Index (BMI) (kg/m2)
- Alcohol consumption (Yes/No)
- Caffeine consumption (Yes/No)
- Tobacco use (Yes/No)

The following Baseline characteristics related to UC reported in the Study APD334-302 will also be summarized by treatment group:

- Extent of disease (Proctosigmoiditis, Left-sided colitis, Pancolitis, Proctitis reported on the electronic case report form [eCRF], and Proctitis reported from Bioclinica Central Read) at APD334-302 study entry
- Baseline MMS
- Baseline rectal bleeding (RB) subscore
- Baseline stool frequency (SF) subscore
- Baseline endoscopic subscore
- Baseline physician's global assessment (PGA)
- Baseline TMS
- Duration of UC (years)
- Any acute exacerbations within past 12 months prior to APD334-302 study entry (Yes/No), including the number of acute exacerbations among those with any acute exacerbation = Yes
- Colonoscopy within past 12 months prior to APD334-302 study entry (Yes/No)
- Surgery for UC (Yes/No) at APD334-302 study entry, including the number of surgeries among those with surgery for UC = Yes
- Hospitalizations for UC (Yes/No), including the number of hospitalizations at APD334-302 study entry
- Naïve to biologic/JAK inhibitor therapy at APD334-302 study entry (Yes/No) – Reported (used for stratification at randomization)
- Naïve to biologic/JAK inhibitor therapy at APD334-302 study entry (Yes/No) – Actual (medications reported on the eCRF)
- Baseline Corticosteroid use (Yes/No) – Reported (used for stratification at randomization)

- Baseline Corticosteroid use (Yes/No) – Actual (medications reported on the eCRF)
- Baseline MMS group (4 to 6, 7 to 9) – Reported (used for stratification at randomization)
- Baseline MMS group (4 to 6, 7 to 9) – Actual (scores reported on the eCRF)
- Naïve to biologic/JAK inhibitor therapy at APD334-302 study entry – Difference between the Reported and the Actual
- Baseline Corticosteroid use (Yes/No) – Difference between the Reported and the Actual
- Baseline MMS group (4 to 6, 7 to 9) – Difference between the Reported and the Actual
- Prior failure of oral 5-ASA only (Yes or No)
- Prior failure of anti-TNFα (Yes or No)
- Prior failure of anti-TNFα or vedolizumab (Yes or No)

Prior treatment for UC will be summarized, including category of treatment, reason for discontinuation, and estimated duration (weeks) of corticosteroid use over the last 12 months.

11.1. Derivations

- Duration of UC (year) = (Informed consent date at APD334-302 – Date of diagnosis + 1) / 365.25
- Weight (kg) = Weight (lb) × 0.4536
- Height (cm) = Height (in) × 2.54
- Height (m) = Height (in) × 0.0254 = Height (cm) × 0.01
- BMI (kg/ m2) = weight (kg)/ height (m)2

12. MEDICAL HISTORY

Medical history not previously collected in Study APD334-302 will be collected on the medical history eCRF and coded using Medical Dictionary for Regulatory Activities (MedDRA, v24.1). The version used to code medical history will be displayed in the outputs. All medical history in APD334-308 will be summarized for the Safety Set by system organ class (SOC) and preferred term (PT).

13. MEDICATIONS AND NON-DRUG TREATMENT

13.1. Medications

Medications will be captured on the Concomitant Medications eCRF and coded using the WHO Drug dictionary (WHODDE01SEP2021). Refer to APPENDIX 2 for handling of partial dates for medications. In the case where it is not possible to define a medication as prior or concomitant, the medication will be classified by the worst case (ie, concomitant).

- 'Prior' medications are medications which started and stopped prior to the first dose of study treatment in study APD334-302.
- 'Concomitant' medications in study APD334-308 are medications which started prior to, on or after the first dose of study treatment in APD334-308 AND ended on or after the date of first dose of study treatment in APD334-308 or were ongoing at the end of this study.

All medications will be listed. Concomitant medications in ADP334-308 that continue from the Study APD334-302 will be flagged in the listing.

13.2. Non-Drug Treatment

Non-drug treatment will be captured on the Concomitant Non-drug treatment eCRF and coded using MedDRA Version 23.1 or newer.

- 'Prior' medications are medications which started and stopped prior to the first dose of study treatment in Study APD334-302.
- 'Concomitant' medications in study APD334-308 are medications which started prior to, on or after the first dose of study treatment in APD334-308 AND ended on or after the date of first dose of study treatment in APD334-308 or were ongoing at the end of this study.

Concomitant non-drug treatment in ADP334-308 will be reported in listing and those continue form the Study APD334-302 will be flagged in the listing.

14. STUDY TREATMENT EXPOSURE

The date of first and last study treatment administration in Study APD334-308 will be taken from eCRF. Interruptions, compliance, and dose changes are taken into account for duration of exposure. Exposure to study treatment in weeks will be summarized for the Safety Set.
Dose interruptions will be recorded on the Dosing Administration eCRF, and overdose will be recorded on the Overdose eCRF. The frequency and percentage of subjects who had at least one dose interruption, who had at least 1 dose interruption of > 7 days, who had at least 1 dose interruption of > 14 days, who had 1 overdose, and who had > 1 overdose will be summarized.

14.1. Derivations

Duration of exposure (weeks) in Study APD334-308 = (date of last study treatment administration – date of Week 12 study treatment administration in Study APD334-302 + 1) / 7.
For subjects with missing Date of Last Dose on the End of Study eCRF, their date of last study treatment administration will be imputed by the last date of all dosing administration start/stop dates recorded.

15. STUDY TREATMENT COMPLIANCE

The total number of tablets expected, total number of tablets taken, total number of tablets missed, overall compliance with study treatment, frequency and percentage of subjects with overall compliance of < 80% or > 120% will be summarized for the Safety Set of APD334-308.

15.1. Derivations

Compliance to study treatment is based on the Drug Accountability eCRF and will be calculated as the total number of tablets taken (total dispensed – total returned) divided by the number of tablets expected during the treatment period, expressed as a percentage, refer to calculations below.
The total number of tablets expected is defined as the number of tablets that a subject is expected to have taken between their first and last study treatment administration and is numerically identical to the subject's overall study treatment exposure, since the medication is to be taken once daily. On any site visit day, the medication is to be held and taken at the site, after all predose assessments have been completed. For example, if a subject took their last dose of study treatment on Day 200 and returned to the site on Day 207 to return the study treatment bottle, then the total number of tablets expected would be 200, not 206.

- Overall compliance to study treatment will be calculated as follows: The total number of tablets returned subtracted from total number of tablets dispensed, divided by the duration of treatment, multiplied by 100

For all bottles not returned, it will be assumed that all dispensed tablets were taken. For each subject, if a high percentage (> 25%) of bottles were not returned by a subject, additional analyses may be done where bottles not returned are excluded from the overall compliance calculation for the subject. In such analysis, the date of last dose or the date of last bottle return, whichever is earlier, will be used as the "date of last dose" in the calculation above.
Both scheduled and unscheduled study treatment dispensations will be used in the compliance calculation. Overall compliance calculations will be performed for the study of APD334-308 and will be used in determining inclusion/exclusion of subjects in the respective Per Protocol Set.

16. EFFICACY OUTCOMES

Unless otherwise stated, the primary efficacy analyses will be based on subject stratum used at the time of randomization in Study APD334-302 for the FAS. Primary and key secondary efficacy analyses will be repeated for all subjects. The following definitions will be used to assess efficacy outcomes:

- Clinical response: A ≥ 2 point and ≥ 30% decrease from Baseline in MMS, and a ≥ 1-point decrease from Baseline in RB subscore or an absolute RB subscore ≤ 1
- Clinical remission: SF subscore = 0 (or = 1 with a ≥ 1-point decrease from Baseline), RB subscore = 0, and ES ≤ 1 (excluding friability)
- Endoscopic improvement: ES of ≤ 1 (excluding friability)
- Endoscopic normalization: ES = 0
- Mucosal healing: ES of ≤ 1 (excluding friability) with histologic remission measured by a Geboes Index score < 2.0
- Symptomatic remission: SF subscore = 0 (or = 1 with a ≥ 1 point decrease from Baseline) and RB subscore = 0
- Complete symptomatic remission: SF subscore = 0 and RB subscore of 0
- Symptomatic response: Decrease from Baseline ≥ 30% in both RB and SF subscores
- Noninvasive clinical response: A ≥ 30% decrease from Baseline in composite RB and SF, and a ≥ 1 point decrease from Baseline in RB subscore or an absolute RB subscore ≤ 1
- CCI [redacted]

- Corticosteroid free clinical remission: Clinical remission at Week 52, while not receiving corticosteroids for 12 or more weeks in the 40 Week Treatment Period
- Sustained clinical remission: Clinical remission at both Week 12 and Week 52
- Loss of response:
  - Achieved clinical response at Week 12 in Study APD334-302
  - A ≥ 2-point increase from Week 12 in the combined SF + RB scores and combined SF + RB score of ≥ 4, on 2 consecutive visits (≥ 7 days apart), and
  - Confirmed by centrally read ES ≥ 2 and,
  - Exclusion of other causes for loss of response unrelated to underlying UC (eg, infection)

16.1. Primary Efficacy

16.1.1. Primary Efficacy Variable and Derivation

The primary efficacy endpoints will compare etrasimod to placebo for:

- The proportion of subjects achieving clinical remission at Week 52

Clinical remission is defined in Section 15. The SF, RB, and ES subscores will be based on the Mayo Clinic Score eCRF. Subjects who achieve clinical remission will be referred to as responders. Subjects who do not achieve clinical remission will be referred to as non-responders.

There will be no adjustments for multiplicity as discussed in Section 8.4.

16.1.2. Missing Data Methods for Primary Efficacy Variable

Subjects who 1) discontinue the study for lack of efficacy, or adverse event related to UC, 2) initiate a rescue medication for UC, 3) have an increase in dose over Baseline levels in their existing UC medication, or 4) have rescue medical procedure (e.g., colectomy, ileostomy, or sigmoidectomy) during the study as confirmed after blinded review by clinical and medical team members before study unblinding will be considered to have a known (i.e., non-missing) outcome of nonresponse in the analysis of all efficacy endpoints at any subsequent timepoints, including the primary endpoint. The rescue medications will be identified by the Arena clinical team during blinded data review. Refer to APPENDIX 6APPENDIX 6 for the definition of rescue therapies (medication and medical procedures). In scenarios #2 and #3 above, if a subject has efficacy measurement collected after the initiation or dose increase from Baseline of UC medication, the observed data will be censored at the time of initiation or dose increase and they will be considered having a nonresponse. Subjects in all 4 scenarios above may still be included in the respective Per Protocol Set, provided they do not violate other criteria for Per Protocol Set. For example, they will be excluded from the respective Per Protocol Set if they initiate a prohibited medication before Week 52 efficacy assessment that can affect efficacy of the study

treatment and the indication is unrelated to UC.
Analysis visits will be mapped as per Section 6.4 before any missing data imputation method is applied.
Subjects with missing efficacy outcome will be included in the primary analyses using single imputation as nonresponder. Supplementary analyses of efficacy outcomes will be performed in modified Full Analysis Set with data as observed.

16.1.3. Primary Analysis of Primary Efficacy Variable

The primary efficacy analysis will be performed for the FAS. Results will be expressed as the number and percentage of subjects in remission, difference in remission percentages and 95% CI and nominal p-value from Fisher's Exact test, odds ratio and 95% CI.

16.1.4. Supplementary Analysis of Primary Efficacy Variables

The primary analysis as described in Section 16.1.3 will be repeated using the mFAS (with data as observed) as supplementary analyses.

Key Secondary Efficacy

Key secondary efficacy endpoints are defined in Section 16.2. In general, all the primary and supplementary analyses planned for the primary endpoints in Section 16.1.3 and Section 16.1.4 will be repeated for each key secondary efficacy endpoint (Table 3). No Multiplicity adjustments will be conducted as discussed in Section 8.4.

Table 3 Planned Analyses by Endpoint

Endpoint	Primary Analysis in FAS	Supplementary Analyses in mFAS
Primary endpoint: Clinical remission at Week 52	X	X
Key secondary endpoints:		
Endoscopic improvement at Week 52	X	X
Symptomatic remission at Week 52	X	X
Corticosteroid-free clinical remission at Week 52	X	X
Mucosal healing at Week 52	X	X
Sustained clinical remission at Week 12 and at Week 52	X	X

16.1.5. Key Secondary Efficacy Variables and Derivations

- Endoscopic Improvement at Week 52.
- Symptomatic Remission at Week 52.

- Corticosteroid-Free Clinical Remission at Week 52.
- Mucosal Healing at Week 52.
- Sustained Clinical Remission (*i.e.*, at both Week 12 in APD334-302 and Week 52 in APD334-308).

There is no multiplicity adjustment in examining any of the key secondary efficacy variables and derivations stated above.

16.1.6. Missing Data Methods for Key Secondary Efficacy Variables

In general, the same missing data methods used for the primary endpoints in Section 16.1.2 will be used for the key secondary endpoints.

16.1.7. Primary Analysis of Key Secondary Efficacy Variables

The primary analysis of these key secondary efficacy endpoints will be performed for the FAS. For all key secondary endpoints, the model described in Section 16.1.3 will be used.

16.1.8. Supplementary Analysis of Key Secondary Efficacy Variables

For all key secondary endpoints, the primary model as described in Section 16.1.3 Section will be repeated using the mFAS (with data as observed) as supplementary analyses.

16.2. Other Secondary Efficacy Variables and Derivations

Other secondary efficacy endpoints are defined in Section 16.

- The proportion of subjects achieving clinical response at Week 52
- The proportion of subjects achieving endoscopic normalization at Week 52
- The proportion of subjects achieving symptomatic remission at Weeks 16, 20, 24, 32, 40, 48 and 52
- The proportion of subjects achieving complete symptomatic remission at each study visit (Weeks 16, 20, 24, 32, 40, 48, and 52)
- The proportion of subjects achieving noninvasive clinical response at each study visit (Weeks 16, 20, 24, 32, 40, 48, and 52)
- The proportion of subjects achieving symptomatic response at each study visit (Weeks 16, 20, 24, 32, 40, 48, and 52)

16.2.1. Missing Data Methods for Other Secondary Efficacy Variables

All subjects with missing data, regardless of reason for missingness, will be considered as nonresponders. The intercurrent events that are considered in the primary efficacy analysis will be handled similarly for the other secondary efficacy endpoints, as specified in Section 16.1.2.

16.2.2. Analysis of Other Secondary Efficacy Variables

The analysis of other secondary efficacy endpoints will be performed for the FAS. The primary analysis method planned for the primary endpoints in Section 16.1.3 will be repeated for each other secondary efficacy endpoint.

CCI [redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

CCI [redacted]

17. HEALTH-RELATED QUALITY OF LIFE AND HEALTHCARE RESOURCE UTILIZATION ANALYSIS

Subject reported HRQoL instruments will be electronically captured and used in support of the efficacy outcomes. All HRQoL are administered at Week 52/Early Termination Visit. The HRQoL analyses will be performed using the mFAS data as observed.
All HRQoL endpoints will be analyzed using descriptive statistics (n, mean, SD, median, minimum, and maximum)
Healthcare resource utilization endpoints, ie, the proportion of concomitant UC-related hospitalizations and the proportion of concomitant UC-related surgeries, including colectomy, will be analyzed using the analysis method described in Section 16.1.3.

17.1. VARIABLES & DERIVATIONS

17.1.1. INFLAMMATORY BOWEL DISEASE QUESTIONNAIRE [IBDQ]

The IBDQ is a 32-item self-administered questionnaire which has 4 dimensions: bowel symptoms (10 items), systemic symptoms (5 items), emotional health (12 items), and social function (5 items). Responses are graded on a 7-point Likert scale where 7 denotes “not a problem at all” and 1 denotes “a very severe problem”. Scores range from 32 to 224, a higher score indicates better quality of life.

The IBDQ total score and 4 domain subscores will be derived on the eCRF directly. Details about scoring rules can be found in APPENDIX 3.

17.1.2. 36-ITEM SHORT FORM HEALTH SURVEY, VERSION 2

The 36-Item Short Form Health Survey (SF-36) is a 36 item, subject-reported survey of subject health. The SF-36 consists of 36 questions measuring 8 health domains: Physical functioning, bodily pain, role limitations due to physical problems, role limitations due to emotional problems, general health perceptions, mental health, social function, and vitality. The subject’s responses are solicited using Likert scales that vary in length, with 3 to 6 response options per item. The SF-36 will also be scored using 2 overall summary scores: Physical component summary (PCS) and mental component summary (MCS) scores. A higher score indicates better health status.

The Physical Component Summary Score (norm based), the Mental Component Summary Score (norm based), 8 domain subscores (0 to100 based), and the SF-6D health utility index score are derived by Optum and integrated into the SF-36 eCRF. Details about domain scores can be found in APPENDIX 4.

17.1.3. WORK PRODUCTIVITY AND ACTIVITY IMPAIRMENT QUESTIONNAIRE – ULCERATIVE COLITIS

The Work Productivity and Activity Impairment Questionnaire – Ulcerative Colitis (WPAI-UC) consists of 6 questions asking about the effect of UC on the subject's ability to work and perform regular activities.
The percent work time missed due to problem (absenteeism), percent impairment while working due to problem (presenteeism), percent overall work impairment due to problem, and percent activity impairment due to problem are derived on the eCRF directly. Details about derivations can be found in APPENDIX 7.

17.1.4. URGENCY NUMERIC RATING SCALE [NRS]

The urgency NRS is a single item that measures the severity for the urgency (sudden or immediate need) to have a bowel movement in the past 24 hours using an 11-point NRS ranging from 0 (no urgency) to 10 (worst possible urgency).

17.1.5. ABDOMINAL PAIN NRS

The abdominal pain NRS is a single item that measures the "worst abdominal pain in the past 24 hours" using an 11-point NRS ranging from 0 (no pain) to 10 (pain as bad as can imagine).

17.1.6. UC-RELATED HOSPITALIZATIONS AND SURGERIES

The UC-related hospitalizations will be captured on the Adverse Event eCRF. The UC-related surgeries, including colectomy, are captured on the Non-Drug Treatment eCRF. Blinded review of AE preferred terms will be performed to determine UC-related hospitalizations.
The UC-related surgeries, including colectomy, will be captured on the Concomitant Non-Drug Treatment eCRF.

17.2. MISSING DATA METHODS

No missing data will be imputed for HRQoL endpoints.

18. Safety Outcomes

All safety outcomes will be based on the Safety Analysis Set. There will be no statistical comparisons between the treatment groups for safety data, unless otherwise specified.

18.1. Adverse Events

Adverse Events (AEs) will be coded using MedDRA (version 24.1). The version used to code AEs will be displayed in the analyses. Treatment emergent adverse events (TEAEs) are defined as AEs that started or worsened in severity on or after the first dose of study treatment in Study APD334-308.

An event that was on-going at end of APD334-302 will be reported in APD334-308 only if it became worsened (increase in severity) after the first dose of study treatment in Study APD334-308. In an integrated report combining APD334-302 and APD334-308 data, this event will be counted only once.

Refer to APPENDIX 2 for handling of partial dates for AEs for the purpose of assigning treatment-emergent flags. In the case where it is not possible to define an AE as treatment emergent or not, the AE will be classified as treatment emergent.

18.1.1. All TEAEs

All TEAEs will be summarized by SOC and PT and presented by descending frequency in the etrasimod group. All AEs, regardless of treatment-emergent status, will be included in an AE listing. Additionally, a listing of other AE details as collected on the CRF will be presented.

Exposure-adjusted incidence rate (EAIR) of TEAEs will be summarized by SOC and PT. Exposure is defined as the sum of either time (year) from first dose in Study APD334-308 to the onset of first such event for those who experienced this AE in Study APD334-308, or time (year) from first dose in Study APD334-308 to last participation for those who did not experience this AE. The EAIR is calculated as the number of subjects with the AE divided by the total exposure in subject-years.

18.1.1.1. Severity

Severity is classified as Grade 1: Mild, Grade 2: Moderate, Grade 3: Severe, Grade 4: Life Threatening, Grade 5: Death Related to AE, using the Common Terminology Criteria for Adverse Events, version 5.0 (CTCAE v5.0).
All TEAEs will be summarized by SOC, PT, and maximum severity, with SOC and PT presented by descending frequency. If a subject reports a TEAE more than once within a SOC/PT, the AE with the worst-case severity will be used in this summary.

18.1.1.2. Relationship to Study Treatment

Relationship is classified as “not related”, “unlikely related”, “probably related”, or “related” by the Investigator.
All related TEAEs will be summarized by SOC and PT. A “related TEAE” for the purpose of this summary is defined as a TEAE with relationship to study drug of “probably related” or

"related".
All TEAEs will be summarized by SOC, PT, and highest relationship (as reported on the eCRF, not grouped), with SOC and PT presented by descending frequency. If a subject reports a TEAE more than once within a SOC/PT, the AE with the worst-case relationship to study treatment will be used in this summary. TEAEs with a missing relationship to study treatment will be regarded as "Related" to study treatment for summary tabulation purpose only.

18.1.2. TEAEs Leading to Discontinuation of Study Treatment

TEAEs leading to discontinuation of study treatment will be identified by action taken being recorded as "Drug withdrawal" on the Adverse events eCRF.
All TEAEs leading to discontinuation of study treatment will be summarized by SOC and PT. A listing of all TEAEs leading to discontinuation of study treatment will also be presented.

Liver-related AEs are defined by either SOC of hepatobiliary disorders or PT of alanine aminotransferase abnormal, alanine aminotransferase increased, aspartate aminotransferase abnormal, aspartate aminotransferase increased, hepatic enzyme abnormal, hepatic enzyme increased, liver function test abnormal, liver function test increased, transaminases abnormal, or transaminases increased.

18.1.3. Serious and Non-Serious TEAEs

Serious adverse events (SAEs) are those events recorded as "Serious" on the Adverse Events page of the eCRF. A summary of serious TEAEs by SOC and PT will be prepared.
All serious TEAEs will be summarized by SOC and PT. If the seriousness is missing, the AE will be considered as "Serious" for the summary tabulation purpose only. A serious TEAE listing will also be presented. All non-serious TEAEs will also be summarized by SOC and PT.

18.1.4. TEAEs Leading to Death

TEAEs leading to Death are those events which are recorded with an outcome as "Fatal" on the Adverse Events eCRF. A listing of TEAEs leading to death will be presented.

18.1.5. TEAEs of Special Interest

Categories of Targeted Medical Events (TMEs) and a list of preferred terms associated with these TME categories were developed based on the mechanism of action of etrasimod, prior experience with other agents acting via a similar mechanism, and disease-specific clinical judgment. In addition, where standard testing has been implemented to screen for potential AESI (eg, electrocardiograms, spirometry, serum transaminases, etc.), the relevant data will be reviewed to identify potential cases of AESI that investigators may not have identified and to provide quantitative data for AESIs. The proposed candidate terms will be reviewed to identify which events reflect AESI.
Treatment-emergent AESIs will be summarized by category, subcategory, and PT by descending frequency by treatment group. Categories and subcategories of TEAEs of special interest are the

following:

- Cardiovascular Events
  - Bradycardia
  - AV conduction delay
  - Hypertension
- Macular Edema
- Pulmonary Disorders
  - Airflow obstruction (forced expiratory volume in 1 second [FEV1], forced vital capacity [FVC])
  - Decrease gas exchange (diffusing capacity of the lungs for carbon monoxide [DLCO])
- Infections
  - Severe infections
  - Opportunistic infections (Narrow)
  - Herpes simplex and herpes zoster
- Liver Injury
  - Liver transaminases elevation
  - Bilirubin elevation
- Posterior Reversible Encephalopathy Syndrome (PRES)
- Malignancies

Exposure-adjusted incidence rate of AESI by category, by subcategory and by PT with 95% CI, and rate difference from placebo and 95% CI will be reported in an integrated analysis combining APD334-302 and APD334-308 data.

18.1.6. Overall Summary of Adverse Events

In addition to the summaries above, an overview of TEAEs will be summarized (not broken down by SOC or PT) by number and percentage of subjects and by number of AEs:

- Any TEAEs
- Any related TEAEs
- Any serious TEAEs
- Any related serious TEAEs
- TEAEs leading to death

- Liver-related TEAEs leading to death
- TEAEs leading to study drug discontinuation
  - Related TEAEs leading to study drug discontinuation
  - Liver-related TEAEs leading to study drug discontinuation
- TEAEs leading to study drug interruption
  - Related TEAEs leading to study drug interruption
- TEAEs by maximum severity
  - Related TEAEs by maximum severity
- TEAEs by relationship to study drug

*Related TEAEs' refers to TEAEs related or probably related to study drug.
Comparative analyses will be performed for:

- Deaths
- Serious TEAEs
- TEAEs leading to study treatment discontinuation
- TEAEs of special interest
- Serious infections
- Opportunistic infections (Narrow)
- Malignancies

18.2. Deaths

Information collected about deaths (e.g., date of death, primary cause of death) will be presented in a data listing, as described in Section 18.1.4.

18.3. Laboratory Evaluations

No local laboratory assessments will be used in any summaries except for lipid panel and thyroid panel tests. No local laboratory assessments will be used to derive maximum/minimum/worst value. Local laboratory assessments will only be listed.

18.3.1. Safety Laboratory Evaluations

Hematology, serum chemistry, coagulation, and urinalysis are analyzed and reported by central laboratory and sometimes by local laboratory. Results out of reference range are flagged by the performing laboratory (e.g., low, high). A full list of laboratory assessments to be included in the outputs is included in Clinical Study Protocol APD334-308 Table 7.

In general, presentations will use SI Units. Quantitative laboratory measurements reported as "< X" or "> X", where X may be the lower limit of quantification (LLQ) or the upper limit of quantification (ULQ), respectively, will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e. as "< X" or "> X" in the listings. For urinalysis, only pH and specific gravity are considered as quantitative tests. If local and central laboratory assessments are available from the same day, central laboratory assessments will be used in the summary as per Section 18.3.1.
The following summaries will be provided for laboratory data:

- Value and change from Baseline by visit (for hematology, serum chemistry, quantitative urinalysis [pH and specific gravity], and coagulation)
- Incidence of abnormal values according to laboratory reference ranges by visit
- Incidence of lymphocytes < 0.2 x 10^9/L, 0.5 x 10^9/L, or neutrophils < 0.5 x 10^9/L, 1 x 10^9/L at Week 52 and anytime after first dose in Study APD334-308
- Shift from end of treatment to each followup visit in incidence of lymphocytes in normal range and in incidence of lymphocytes of at least 80% percent of Baseline, by visit (2-Week Follow-Up, 4-Week Follow-Up, and Last FollowUp)Shift from Baseline to Week 52/Early Termination Visit according to laboratory reference range (for quantitative measurements and categorical measurements)
- Evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) plots for the following laboratory assessments (using values after the first administration of study treatment):
  - Maximum aspartate aminotransferase (AST) versus same-day total bilirubin
  - Maximum alanine aminotransferase (ALT) versus same-day total bilirubin
  - Maximum gamma-glutamyl transferase (GGT) versus same-day total bilirubin
  - Maximum alkaline phosphatase (ALP) versus same-day total bilirubin

  The eDISH plots above will be repeated with adjustment for elevated Baseline.
- Incidence of hepatic enzyme elevations by visit
  - > 1 ×, 2 ×, 3 ×, 5 ×, 8 ×, 10 ×, 20 × upper limit of normal (ULN) elevation in ALT
  - > 1 ×, 2 ×, 3 ×, 5 ×, 8 ×, 10 ×, 20 × ULN elevation in AST
  - > 3 ×, 5 ×, 10 ×, 20 × ULN elevation in either ALT or AST
  - > 1 ×, 1.5 ×, 2 ×, 3 × ULN elevation in total bilirubin
  - > 1 ×, 1.5 ×, 2 ×, 3 ×, 5 ×, 8 × ULN elevation in ALP
  - > 1 ×, 2 ×, 3 ×, 5 ×, 8 × ULN elevation in GGT
  - > 3 × ULN elevation in either ALT or AST and > 1.5 × ULN elevation in total bilirubin
  - > 3 × ULN elevation in either ALT or AST and > 2 × ULN elevation in total

bilirubin
– > 3 × ULN elevation in either ALT or AST and > 1.5 × ULN elevation in ALP
– > 3 × ULN elevation in either ALT or AST in temporal association with treatment-emergent nausea, vomiting, anorexia, abdominal pain, or fatigue identified by PT, where temporal association is defined as ±14 days of onset date from the time of elevation.

If both central and local assessments of total bilirubin are available on the same day, the central result will take precedence over the local result in the eDISH plot. If the maximum AST/ALT/GGT assessment occurs at two 2 different dates, the assessment with the higher accompanying Bilirubin value will be used. Two versions of the eDISH plots will be presented, with one showing values as multiples of upper limit of normal, and the other one showing values as multiples of upper limit of normal, or subject's baseline, whichever is higher.
Subject's laboratory assessments at all timepoints will be listed in chronological order. Values outside of the laboratory reference range will be flagged. Values obtained from local laboratory will be flagged. Listing of lymphocytes and neutrophils over time in subjects ever with lymphocytes <0.5 x 10^9/L or neutrophils < 1 x 10^9/L will also be provided.

18.3.2. Pregnancy Tests

Urine beta-human chorionic gonadotropin (β-hCG) and/or serum β-hCG pregnancy tests are performed throughout the study in female subjects of childbearing potential. All pregnancy test results (positive or negative) will be listed in chronological order.

18.3.3. Other Screening Laboratory Assessments

Screening laboratory assessments for virology, drug screen/toxicology, QuantiFERON Tuberculosis (TB) Gold, stool pathogens, and *Clostridioides difficile* (formerly known as *Clostridium difficile*) will be listed. Analyses of genetics and exploratory efficacy-related biomarkers data based on samples collected at Screening in subjects who provided consent will be described in a separate plan.

18.4. ECG Evaluations

ECGs are recorded on a 12-lead ECG machine and read centrally. The following ECG parameters will be reported for this study:

- HR (bpm)
- RR Interval (msec)
- PR Interval (msec)

- QRS Interval (msec)
- QT Interval (msec)
- QTcF Interval (msec)
- Overall assessment of ECG (Investigator's judgment):
  - Normal
  - Abnormal, Not Clinically Significant (Abnormal NCS)
  - Abnormal, Clinically Significant (Abnormal CS)
- Overall interpretation of ECG (central reader):
  - Normal
  - Abnormal NCS
  - Abnormal CS
- AV conduction abnormalities
  - First-degree AV block
  - Second-degree AV block type 1
  - Second-degree AV block type 2
  - Third-degree AV block

The following summaries will be provided for ECG data:

- Value and change from Baseline by visit (for quantitative measurements)
- Incidence of markedly abnormal values (defined in Section 18.4.1) and AV blocks by visit
- Shift in normal/abnormal NCS/abnormal CS in the overall interpretation (by investigator) from Baseline to Week 52/Early Termination Visit and to the worst-case post-Baseline result
- Shift in markedly abnormal categories from Baseline to post-Baseline by visit

Listings of ECG results, including first dose cardiac monitoring, and discharge criteria for first dose cardiac monitoring will be provided.
A listing of all ECG assessments over time in subjects meeting markedly abnormal criteria will also be provided. For each subject, only ECG parameters ever meeting markedly abnormal criteria will be included.

18.4.1. ECG Markedly Abnormal Criteria

Markedly abnormal quantitative ECG measurements will be identified in accordance with the

following predefined markedly abnormal criteria:

- Absolute values in QT and QTcF:
  - ≥ 450 msec (male) or ≥ 470 msec (female) in QTcF
  - > 500 msec in QT
- Change from Baseline in QT and QTcF:
  - > 30 msec increase from Baseline
  - > 60 msec increase from Baseline

In shift tables, subjects will be classified according to the binary category for each parameter and the predefined markedly abnormal criterion (i.e., Markedly abnormal vs. Not markedly abnormal).

18.5. Vital Signs

The following vital signs measurements will be reported for this study:

- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)
- Heart Rate (bpm)
- Respiratory Rate (resp/min)
- Temperature (ºC)

The following summaries will be provided for vital signs data:

- Value and change from Baseline by visit
- Value and change from predose on Day 1 (as reported on the eCRF) by timepoint
  - For heart rate only, value and change from predose to minimum postdose heart rate on Day 1 will be included in the same table
- Incidence of markedly abnormal values (defined in Table 4) by visit, including anytime after first dose in Study APD334-308
- Listing of subjects meeting markedly abnormal criteria
- Incidence of minimum heart rate on Day 1 in Study APD334-302 by postdose timepoint (1, 2, 3, 4, and > 4 hours postdose, and Day 1 overall) and heart rate interval (≥ 65, 60 to 64, 55 to 59, 50 to 54, 45 to 49, 40 to 44, < 40 bpm)
  - If minimum heart rate is attained at multiple postdose timepoints, only the earliest timepoint will be counted in this incidence summary.

- Time to minimum heart rate on Day 1 in Study APD334-302 by planned hourly timepoint (if minimum heart rate is attained at multiple postdose timepoints, only the earliest timepoint will be counted).
  - Actual time elapsed from first dose to minimum heart rate on Day 1 will also be summarized using descriptive statistics (n, mean, SD, median, minimum, and maximum) in the same table.
- Line plots for mean value and mean change from predose on Day 1 in Study APD334-302, up to 4 hours postdose by parameter and timepoint (systolic blood pressure, diastolic blood pressure, and heart rate)
- Line plots for mean value and mean change from Baseline by parameter and visit (systolic blood pressure, diastolic blood pressure, heart rate, body temperature, and respiratory rate)

Listings of all vital signs, including first dose cardiac monitoring, and discharge criteria for first dose cardiac monitoring will be provided. A listing of vital signs assessments over time in subjects meeting a markedly abnormal criterion will also be provided. For each subject, only the parameters with at least one markedly abnormal criterion satisfied will be included.
For subjects with extended monitoring or remonitoring, a listing of systolic blood pressure, diastolic blood pressure, heart rate values, and change from predose in all parameters on Day 1, Day 2, and any remonitoring visit will be provided.

18.5.1. Vital Signs Specific Derivations

- Temperature (°C) = (5/9) (Temperature (°F) – 32)

18.5.2. Vital Signs Markedly Abnormal Criteria

Markedly abnormal quantitative Vital Signs measurements will be identified in accordance with the following predefined markedly abnormal criteria:

Table 4 Markedly Abnormal Criteria for Vital Signs

Variable	Unit	Low	High
SBP	mmHg	≤ 90 mmHg	> 150 mmHg
DBP	mmHg	≤ 50 mmHg	> 90 mmHg
Heart rate	bpm	< 40 bpm < 50 bpm < 50 bpm and decrease from predose (Baseline) of > 10 bpm at 4 hours on Day 1 or Day 2 or remonitoring visit	>100 bpm

bpm, beats per minute; DBP, diastolic blood pressure; SBP, systolic blood pressure.

18.6. Physical Examination

A listing of all physical examination assessments in subjects who had at least 1 abnormal finding.

18.7. Other Safety Assessments

18.7.1. Pulmonary Function Tests

The following pulmonary function test (PFT) measurements (actual and % Predicted) will be reported for this study:

- FEV_1
- FVC
- Total Lung Capacity (TLC)
- FEV_1/FVC ratio
- Forced Expiratory Flow (FEF) 25-75
- DLCO (if available)

The following summaries will be provided for PFT data:

- Value and change from Baseline by visit
- Incidence of markedly abnormal values by visit (Section 18.7.1)

All PFT data will be listed. A listing in subjects who ever reported an abnormality in PFT will also be provided, including a flag for whether markedly abnormal criterion is also met.

18.7.1.1. PFT Markedly Abnormal Criteria

Markedly abnormal quantitative PFT measurements will be identified in accordance with the following predefined markedly abnormal criteria:

- • % Predicted $FEV_1 < 50\%$
- • % Predicted FVC < 50%
- • % Predicted FEV_1/FVC ratio < 50%

Potentially important PFT measurements will also be identified using the criteria below:

- • Decrease from Baseline > 20% in FEV_1, ie, percent change from Baseline < -20%
- • Decrease from Baseline > 20% in FVC, ie, percent change from Baseline < -20%
- • Decrease from Baseline > 20% in DLCO, ie, percent change from Baseline < -20%

18.7.2. Ophthalmoscopy And Optical Coherence Tomography [OCT]

The following summaries will be provided for ophthalmoscopy and optical coherence tomography (OCT) data:

- Values and change from Baseline in central foveal thickness and intraocular pressure by visit
- Categorical results in ophthalmoscopy with OCT parameters by visit (the categories are listed on the eCRF)

Only PFT and OCT assessments completed by 50 or more subjects in the Safety Set will be presented in the summaries.
A listing of all ophthalmoscopy and OCT assessments will be provided. A listing of subjects who ever reported an abnormality in OCT will also be provided. Additionally, a listing of retinal photograph and eye pressure assessments will be provided for subjects who experienced an AE related to eye disorders.

18.7.3. Tuberculosis Screening and Chest X-Ray

Screening TB results and chest X-rays will be listed. Results of TB questionnaires will also be listed.

19. Efficacy-RELATED BIOMARKERS

Value and change from Baseline in level of FCP, hs-CRP, and lymphocyte counts at protocol-specified visits will be summarized by visit and treatment for the FAS. Additionally, percent of change from Baseline in lymphocyte counts will also be summarized. Change from Baseline in these biomarkers to Week 12 of ADP334-302 and all scheduled visits up to Week 52 in APD334-308 will also be summarized using descriptive statistics (n, mean, SD, median, minimum, and maximum). Additionally, the following summaries will be provided for biomarker data:

- Line plots over time for mean with 95% CI for the following laboratory assessments:
  - Change from Baseline in lymphocytes
  - Percent change from Baseline in lymphocytes
  - Change from Baseline in hsCRP
  - Change from Baseline in FCP

The exploratory efficacy-related biomarker analyses for immunophenotyping, proteomics, RNA transcriptomics, and fecal microbiome will be described in a separate biomarker analysis plan.

20. Pharmacokinetics

PK samples to access plasma etrasimod concentrations will be collected prior to dosing (trough) at Weeks 16, 20, 24, 32, 40, 48, and 52; and at 2-Week and 4-Week Follow-Up visits for subjects that do not enroll into any extension study. A descriptive summary of observed plasma etrasimod concentration will be displayed by time and treatment group. Summary of observed plasma

etrasimod concentrations by time and treatment group will be repeated by sex (male or female), weight (≤ Median or > Median) and age group (< 18, 18 to < 65, or ≥ 65 years). Concentrations below the limit of quantitation (BLQ) will be assigned a numerical value of zero for the calculation of descriptive statistics. For geometric mean and geometric % coefficient of variation [CV], the zero values will be excluded.

The pharmacokineticist will determine the strategy for dealing with data affected by protocol deviations or events which may impact the quality of etrasimod concentration data on a case-by-case basis with input from the Arena study physician and Arena clinical pharmacologist, as needed. Examples for protocol deviations or events include, but may not be limited to, sample processing errors that lead to inaccurate bioanalytical results, and/or inaccurate dosing prior to PK sampling. In the case of an important protocol deviation or event, the affected PK data collected may be excluded from the summaries, calculation of the average steady-state trough plasma concentration ($C_{trough,ss}$) based on Week 16 to Week 52 trough concentrations ($C_{trough,ss,W16W16W16-W52}$), and population PK analysis, but will be reported in the study result listings.

Individual subject etrasimod plasma concentrations (and etrasimod metabolite concentrations, if applicable) will be presented in the data listings, including subject ID, treatment received, sex, age, weight, tobacco use, nominal timepoint, actual blood collection date/time, concentration, and time since last dose and also summarized using descriptive statistics (n, mean, SD, % CV, geometric mean, geometric % CV, median, minimum, and maximum) by nominal timepoint.

Individual subject steady-state trough (predose) plasma concentration will be averaged across Weeks 16 to 52 ($C_{trough,ss,W16-W52}$) and presented in a data listing and summarized using descriptive statistics.

Mean (± SD) etrasimod concentration versus nominal time (Weeks 16 to 52) will be plotted on linear scales. Plot will be repeated by sex (male and female).

Individual subject plasma etrasimod concentrations versus actual time (Weeks 16 to 52) will be plotted on linear scale.

Scatter plots of individual subject average steady-state $C_{trough\ ss,W2-W52}$ versus Baseline body weight as a continuous variables will be generated for the Pharmacokinetic Set, which will also include the Spearman's rank correlation coefficient, p-value, and locally estimated scatterplot smoothing (LOESS) trend line.

Furthermore, the following overlay plots will be generated for the Pharmacokinetic Set within the etrasimod group only:

- Mean (SD) absolute lymphocyte counts and mean (SD) etrasimod concentration versus nominal timepoint (Weeks 16 through 52)
- Mean (SD) absolute change from Baseline in lymphocytes and mean (SD) etrasimod concentration versus nominal timepoint (Weeks 16 through 52)
- Mean (SD) percent change from Baseline in lymphocytes and mean (SD) etrasimod concentration versus nominal timepoint (Weeks 16 through 52)

- Mean (SD) heart rate and mean (SD) etrasimod concentration versus nominal timepoint (Weeks 16 through 52)
- Mean (SD) absolute change from Baseline in heart rate and mean (SD) etrasimod concentration versus nominal timepoint (Weeks 16 through 52)

The plasma etrasimod concentrations over time will be used in a population PK analysis, etrasimod concentration and specific efficacy endpoints will be used in a population PK/PD exposure-efficacy response analysis and etrasimod concentration and absolute lymphocyte count will be used in a population PK/PD exposure-lymphocyte response analysis, which will be described in a separate plan.

CCI [redacted]

22. References

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APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

IQVIA OUTPUT CONVENTIONS

Outputs will be presented as shown in the Output shells.

DECIMALS AND PERCENTAGES

- If the original data has N decimal places, then the summary statistics should have the following decimal places:
  - Minimum and maximum: N
  - Mean (and LS Means), median: N + 1
  - SD or SE: N + 2
- Percentages will be reported to one decimal place. Where counts are zero, percentages will not appear in the output.

DATES & TIMES

Depending on data available, dates and times will take the form DDMMMYYYY or DDMMMYYYY:hh:mm..

SPELLING FORMAT

English US.

PRESENTATION OF TREATMENT GROUPS

For outputs, treatment groups will be represented as follows and in the given order:

Treatment Group	For Tables, Graphs, and Listings
Etrasimod 2 mg	Etrasimod 2 mg
Placebo	Placebo
Screen Failure	Screen Failure
Not Treated[a]	Not Treated

[a] To be used for subjects in safety listings who are randomized but do not receive study drug.

PRESENTATION OF VISITS

For outputs, visits will be represented as follows and in that order:

Visit Name	Study Period
Eligibility Assessment	Screening
Baseline, Week 12, Week 16, Week 20, Week 24, Week 32, Week 40, Week 48, and Week 52	Treatment
Early Termination	Dependent on Analysis Visit assigned
2-Week Follow-Up, 4-Week Follow-Up	Follow-Up

LISTINGS

All listings will be ordered by the following (unless otherwise indicated in the template):

- Randomized treatment group (or treatment received if it's a safety output), first by Etrasimod, then Placebo, then Not Randomized and then No Treatment (only in safety listings if there are any randomized subjects who did not receive study drug)
- Subject ID,
- Date (where applicable),
- For listings where non-randomized subjects are included, these will appear in a category after the randomized treatment groups labeled 'Not Randomized'.

APPENDIX 2. PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings.

ALGORITHM FOR TREATMENT EMERGENCE OF ADVERSE EVENTS IN STUDY APD334-308:

START DATE	STOP DATE	ACTION
Known	Known/Partial/ Missing	If start date < study drug first dose date in APD334-308, then not TEAE If start date < study drug first dose date in APD334-308 AND event worsened (increase in severity) after first dose date in APD334-308, then TEAE If start date >= study drug first dose date in APD334-308, then TEAE
Partial, but known components show that it cannot be on or after study drug first dose date in APD334-308	Known/Partial/ Missing	Not TEAE
Partial, could be on or after study drug first dose date in APD334-308 OR Missing	Known	If stop date < study drug first dose date in APD334-308, then not TEAE If stop date >= study drug first dose date in APD334-308, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study drug first dose date in APD334-308, then not TEAE If stop date >= study drug first dose date in APD334-308, then TEAE
	Missing	Assumed TEAE

START DATE	STOP DATE	ACTION

ALGORITHM FOR PRIOR / CONCOMITANT MEDICATIONS:

Start Date	Stop Date	Action
Known	Known	If medication stop date < study med first dose date in APD334-308, assign as prior If medication stop date ≥ study med first dose date in APD334-308, assign as concomitant
	Partial	Impute stop date as latest possible date (ie, last day of month if day unknown or 31st December if day and month are unknown), then: If medication stop date < study med first dose date in APD334-308, assign as prior If medication stop date ≥ study med first dose date in APD334-308, assign as concomitant
	Missing	If medication stop date is missing could never be assumed a prior medication, assign as concomitant
Partial	Known	Impute start date as earliest possible date (ie, first day of month if day unknown or 1st January if day and month are unknown), then: If medication stop date < study med first dose date in APD334-308, assign as prior If medication stop date ≥ study med first dose date in APD334-308, assign as concomitant
	Partial	Impute start date as earliest possible date (ie, first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (ie, last day of month if day unknown or 31st December if day and month are unknown), then: If medication stop date < study med first dose date in APD334-308, assign as prior If medication stop date ≥ study med first dose date in APD334-308, assign as concomitant
	Missing	Impute start date as earliest possible date (ie, first day of month if day unknown or 1st January if day and month are unknown), then: If medication stop date is missing could never be assumed a prior medication, assign as concomitant
Missing	Known	If medication stop date < study med first dose date in APD334-308, assign as prior Else assign as concomitant

Start Date	Stop Date	Action
	Partial	Impute stop date as latest possible date (ie, last day of month if day unknown or 31st December if day and month are unknown), then: If medication stop date < study med first dose date in APD334-308, assign as prior If medication stop date ≥ study med first dose date in APD334-308, assign as concomitant
	Missing	Assign as concomitant

APPENDIX 3. **IBDQ SCORING RULES**

The IBDQ is a 32-item self-administered questionnaire which has 4 dimensions: Bowel symptoms (10 items), systemic symptoms (5 items), emotional health (12 items), and social function (5 items). Responses are graded on a 7-point Likert scale where 7 denotes “not a problem at all” and 1 denotes “a very severe problem”. Scores range from 32 to 224, a higher score indicates better quality of life.

The 4 dimensions are defined as:

Bowel symptoms: Questions 1, 5, 9, 13, 17, 20, 22, 24, 26, 29

Systemic symptoms: Questions 2, 6, 10, 14, 18

Emotional health: Questions 3, 7, 11, 15, 19, 21, 23, 25, 27, 30, 31, 32

Social function: Questions 4, 8, 12, 16, 28

APPENDIX 4. SF-36 DOMAIN SCORES

The SF-36 is a 36-item self-administered questionnaire which has 8 scales: Physical functioning (10 items), role limitations due to physical health (4 items), role limitations due to emotional problems (3 items), energy/fatigue (4 items), emotional wellbeing (5 items), social functioning (2 items), pain (2 items), and general (5 items). Each item response is scored from 0 to 100 and items in the same scale are averaged together to create 8 subscores. Scores range from 0 to 100. A higher score indicates a more favorable health state.

The 8 dimensions are defined as:

Physical functioning: Questions 3-12

Role limitations due to physical health: Questions 13-16

Role limitations due to emotional problems: Questions 17-19

Energy/fatigue: Questions 23, 27, 29, 31

Emotional wellbeing: Questions 24-26, 28, 30

Social functioning: Questions 20, 32

Pain: Questions, 21, 22

General health: Questions 1, 33-36

APPENDIX 5. **WPAI-UC SCORING RULES**

The WPAI-UC questionnaire was developed to measure the effect of general health and symptom severity on work productivity and regular activities. The questionnaire includes the following questions.

Questions:

1 = Are you currently employed?
2 = During the past seven days, how many hours did you miss from work due to your problems associated with UC?
3 = During the past seven days, how many hours did you miss from work because of any other reasons?
4 = During the past seven days, how many hours did you actually work?
5 = During the past seven days, how much did your UC affect your productivity while you were working?
6 = During the past seven days, how much did your UC affect your ability to do your regular daily activities, other than work at a job?

Derivation:

1) Calculate work time missed score as: Q2/(Q2+Q4)
2) Calculate impairment while working score as: Q5/10
3) Calculate overall work impairment score as: Q2/(Q2+Q4) + [(1 - Q2/(Q2+Q4)) x (Q5/10)]
4) Calculate activity impairment score as: Q6/10

Multiply each score by 100 in order to express as percentages.

APPENDIX 6. CLASSIFICATION OF RESCUE THERAPY

This appendix outlines the algorithm for the Arena clinical team/medical reviewers to classify rescue therapies for ulcerative colitis (UC) in a blinded manner. This will help establish 1) intercurrent events for the efficacy estimands, and 2) whether a subject will be excluded from the Per Protocol Set(s). All rescue therapies identified by the medical reviewers per the algorithm below will be imported in programming. This process will be repeated until database lock and the list of all rescue therapies identified will be finalized before study unblinding.

Only medications and medical procedures reported on the electronic case report forms (eCRFs) can be assessed whether they are rescue therapy for UC. If the exposure happens in the follow-up period (beginning on or after the date of last study treatment administration), then it would not be considered as a rescue therapy. Impact of rescue therapy use in the analysis is timing-dependent, eg, if a subject starts a rescue therapy between their Week 12 and Week 52 endpoint assessments, then it may have potential impact on Week 52 endpoint analysis but will have no impact on Week 12 endpoints. The rules outlined below apply to both new use and increase in dose from Baseline.

Biologics with immunomodulatory properties

- Rule:
  - Any exposure after first dose
- List of medications
  - Anti-TNFs:
    - ADALIMUMAB
    - CERTOLIZUMAB
    - CERTOLIZUMAB PEGOL
    - GOLIMUMAB
    - INFLIXIMAB
  - Other Biologics:
    - USTEKINUMAB
    - VEDOLIZUMAB

Non-biologics with immunomodulatory properties

- Immunosuppressants
  - Rule to consider for Week 12 efficacy endpoints:
    - After first dose and up to and including Week 8: any increase from baseline for more than 5 days

        - After Week 8: Any dose above baseline
    - Rule to consider for Week 52 efficacy endpoints:
        - After Week 12 and up to and including Week 40: any increase from baseline for more than 5 days
        - After Week 40: Any dose above baseline
    - List of medications
        - MERCAPTOPURINE
        - AZATHIOPRINE
        - TIOGUANINE
        - METHOTREXATE
        - METHOTREXATE SODIUM
- 5-ASA COMPONDS
    - Rules to consider for Week 12 efficacy endpoints:
        - After first dose and up to and including Week 8: any increase from baseline for more than 5 days
        - After Week 8: Any dose above baseline
    - Rules to consider for Week 52 efficacy endpoints:
        - After Week 12 and up to and including Week 40: any increase from baseline for more than 5 days
        - After Week 40: Any dose above baseline
    - List of medications
        - MESALAZINE
        - BALSALAZIDE
        - BALSALAZIDE DISODIUM DIHYDRATE
        - BALSALAZIDE SODIUM
        - OLSALAZINE SODIUM
        - SULFASALAZINE
        - BECLOMETASONE W/MESALAZINE
    - Route
        - ORAL
        - RECTAL

- Other small molecule immunomodulatory active agents
  - Rule:
    - Any exposure after first dose
  - List of medications
    - CICLOSPORIN
    - TACROLIMUS
    - TOFACITINIB
    - TOFACITINIB CITRATE
- Systemic glucocorticoids
  - Systemic glucocorticoids given via oral or rectal routes of administration
    - Rule:
      - After first dose and up to and including Week 8: any increase from baseline for more than 7 days
      - After Week 8: Any dose above baseline
    - List of medications
      - BETAMETHASONE
      - BETAMETHASONE DIPROPIONATE
      - BETAMETHASONE SODIUM PHOSPHATE
      - DEXAMETHASONE
      - DEXAMETHASONE SODIUM PHOSPHATE
      - DEXAMETHASONE VALERATE
      - METHYLPREDNISOLONE
      - METHYLPREDNISOLONE SODIUM SUCCINATE
      - PREDNISOLONE
      - PREDNISOLONE SODIUM PHOSPHATE
      - PREDNISOLONE METASULFOBENZOATE SODIUM
      - PREDNISONE
      - TRIAMCINOLONE
      - HYDROCORTISONE
      - HYDROCORTISONE ACETATE

        - HYDROCORTISONE BUTYRATE
        - HYDROCORTISONE SODIUM SUCCINATE
    - ROUTE
        - ORAL
        - RECTAL
- Systemic glucocorticoids given via parenteral routes of administration
    - Rule:
        - Any exposure after first dose
    - List of medications
        - BETAMETHASONE
        - BETAMETHASONE DIPROPIONATE
        - BETAMETHASONE SODIUM PHOSPHATE
        - DEXAMETHASONE
        - DEXAMETHASONE SODIUM PHOSPHATE
        - DEXAMETHASONE VALERATE
        - METHYLPREDNISOLONE
        - METHYLPREDNISOLONE SODIUM SUCCINATE
        - PREDNISOLONE
        - PREDNISOLONE SODIUM PHOSPHATE
        - PREDNISOLONE METASULFOBENZOATE SODIUM
        - PREDNISONE
        - TRIAMCINOLONE
        - HYDROCORTISONE
        - HYDROCORTISONE ACETATE
        - HYDROCORTISONE BUTYRATE
        - HYDROCORTISONE SODIUM SUCCINATE
    - ROUTE
        - INTRAVENOUS
        - INTRAMUSCULAR
- Topical Glucocorticoids

- Budesonide
  - Rule
    - Subjects not taking Budesonide at baseline:
      - After first dose and up to and including Week 8: more than 9 mg/day for one day or any exposure for more than 5 days
      - After Week 8: Any dose above baseline
    - Subjects taking Budesonide at baseline
      - After first dose and up to and including Week 8: more than 9 mg/day for one day or any increase for more than 5 days
      - After Week 8: Any dose above baseline
  - List of medications
    - BUDESONIDE
  - List of Routes

    ORAL
    - RECTAL

- Beclomethasone
  - Rule
    - Subjects not taking Beclomethasone at baseline:
      - After first dose and up to and including Week 8: more than 5 mg/day for one day OR any exposure for more than 5 days
      - After Week 8: Any dose above baseline
    - Subjects taking Beclomethasone at baseline
      - After first dose and up to and including Week 8: more than 5 mg/day for one day or any increase for more than 5 days
      - After Week 8: Any dose above baseline
  - List of medications:
    - BECLOMETASONE
    - BECLOMETASONE DIPROPIONATE
    - BECLOMETASONE W/MESALAZINE
  - Routes:
    - ORAL
    - RECTAL

- Other small molecule immunomodulatory active agents
  - Rules to consider for Week 12 efficacy endpoints:
    - After first dose and up to and including Week 8: any increase from baseline (including new use) for more than 5 days
    - After Week 8: Any dose above baseline
  - Rules to consider for Week 52 efficacy endpoints:
    - After Week 12 and up to and including Week 40: any increase from baseline (including new use) for more than 5 days
    - After Week 40: Any dose above baseline
  - List of medications:
    - CICLOSPORIN
    - TACROLIMUS
    - TOFACITINIB
    - TOFACITINIB CITRATE
- Systemic glucocorticoids
  - Systemic glucocorticoids given via oral or rectal routes of administration
    - Rules to consider for Week 12 efficacy endpoints:
      - After first dose and up to and including Week 8: any increase from baseline for more than 7 days
      - After Week 8: Any dose above baseline
    - Rules to consider for Week 52 efficacy endpoints:
      - After Week 12 and up to and including Week 40: any increase from baseline for more than 7 days
      - After Week 40: Any dose above baseline
    - List of medications:
      - BETAMETHASONE
      - BETAMETHASONE DIPROPIONATE
      - BETAMETHASONE SODIUM PHOSPHATE
      - DEXAMETHASONE
      - DEXAMETHASONE SODIUM PHOSPHATE
      - DEXAMETHASONE VALERATE

- METHYLPREDNISOLONE
- METHYLPREDNISOLONE SODIUM SUCCINATE
- PREDNISOLONE
- PREDNISOLONE SODIUM PHOSPHATE
- PREDNISOLONE METASULFOBENZOATE SODIUM
- PREDNISONE
- TRIAMCINOLONE
- HYDROCORTISONE
- HYDROCORTISONE ACETATE
- HYDROCORTISONE BUTYRATE
- HYDROCORTISONE SODIUM SUCCINATE

  - Routes:
    - ORAL
    - RECTAL

- Systemic glucocorticoids given via parenteral routes of administration
  - Rule for Week 12 endpoint:
    - Any exposure after first dose up to Week 12
  - Rules for Week 52 endpoint:
    - After Week 12 and up to and including Week 40: more than one dose
    - Any exposure after Week 40
  - List of medications:
    - BETAMETHASONE
    - BETAMETHASONE DIPROPIONATE
    - BETAMETHASONE SODIUM PHOSPHATE
    - DEXAMETHASONE
    - DEXAMETHASONE SODIUM PHOSPHATE
    - DEXAMETHASONE VALERATE
    - METHYLPREDNISOLONE
    - METHYLPREDNISOLONE SODIUM SUCCINATE
    - PREDNISOLONE

        - PREDNISOLONE SODIUM PHOSPHATE
        - PREDNISOLONE METASULFOBENZOATE SODIUM
        - PREDNISONE
        - TRIAMCINOLONE
        - HYDROCORTISONE
        - HYDROCORTISONE ACETATE
        - HYDROCORTISONE BUTYRATE
        - HYDROCORTISONE SODIUM SUCCINATE
    - Routes:
        - INTRAVENOUS
        - INTRAMUSCULAR
- Topical Glucocorticoids
    - Rules for Week 12 endpoints:
        - After first dose and up to and including Week 8: any exposure above baseline (or new use) for more than 5 days
        - After Week 8: Any dose above baseline
    - Rules for Week 52 endpoints:
        - After Week 12 and up to and including Week 40: any increase from baseline for more than 5 days
        - After Week 40 any increase above baseline
    - List of medications:
        - BUDESONIDE
    - Routes:
        - ORAL
        - RECTAL
- Beclomethasone
    - Rules for Week 12 endpoints:
        - After first dose and up to and including Week 8: Any increase above baseline for more than 5 days
        - After Week 8: Any dose above baseline
    - Rules for Week 52 endpoints:

- After Week 12 and up to and including Week 40: Any increase from baseline for more than 5 days
- After Week 40 any increase above baseline

- List of medications:
  - BECLOMETASONE
  - BECLOMETASONE DIPROPIONATE
  - BECLOMETASONE W/MESALAZINE
- Routes:
  - ORAL
  - RECTAL

Medical procedures

- Leukocyte apheresis, other apheresis, and plasma exchange
  - Rule:
    - Any exposure after first dose
  - List of medical procedures
    - APHERESIS
    - LEUKAPHERESIS
    - COLECTOMY (partial or total)
    - SIGMOIDECTOMY
    - COLOSTOMY
    - ILEOSTOMY

Electronic Signature Manifestation

This page is a manifestation of the electronic signature(s) used in compliance with the organization's electronic signature policies and procedures.

Signer Full Name	Meaning of Signature	Date and Time
PPD	Document Approval (I certify that I have the education, training and experience to perform this task)	27 Sep 2022 23:50:22 UTC
PPD	Document Approval (I certify that I have the education, training and experience to perform this task)	28 Sep 2022 00:04:48 UTC
PPD	Document Approval (I certify that I have the education, training and experience to perform this task)	28 Sep 2022 10:56:10 UTC